UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte QINJIAN ZHAO, ROBERT SITRIN, DICKY G. ABRAHAM DAVID P. GERVAIS and JUAN GIMENEZ

Appeal No. 2005-1171
Application No. 09/469,485

ON BRIEF

ELLIS, SCHEINER and GRIMES, Administrative Patent Judges.

ELLIS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal pursuant to 35 U.S.C. § 134 from the examiner's final rejection of claims 8-20, all the claims pending in the application. Claims 1-7 have been cancelled.

Claim 8 is representative of the subject matter on appeal and reads as follows:

8. A method of increasing the antigenicity of recombinant hepatitis B surface antigen (rHBsAg) comprising:

a) providing soluble sterile filtered rHBsAg purified from a cell culture,

b) adding a redox buffer to the rHBsAg,

c) adjusting the temperature to about 34° C to about 38° C,

d) incubating the rHBsAg at about 34° C to about 38° C for about 40 to about 240 hours, wherein the antigenicity of the rHBsAg produced after step d is greater than the antigenicity of the rHBsAg provided in step a.

The references relied upon by the examiner are:

Even-Chen	5,242,812	Sep. 7, 1993
Builder et al. (Builder)	4,620,948	Nov. 4, 1986
Petre et al. (Petre)	WO 93/24148	Dec. 9, 1993

Valenzuela et al. (Valenzuela), "Nucleotide sequence of the gene coding for the major protein of hepatitis B virus surface antigen," Nature, vol. 280, pp. 815-819, (1979).

The claims stand rejected as follows:

I. Claims 8-16 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Builder and Valenzuela.

II. Claims 17, 19 and 20 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Builder and Valenzuela as applied to claims 8-16 above, and further in view of Petre.

III. Claim 18 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Builder and Valenzuela as applied to claims 8-16 above, and further in view of Even-Chen.

We reverse.

Discussion

As indicated by claim 8 above, the appellants' invention is said to be directed to increasing the antigenicity of recombinant hepatitis B surface antigen (rHBsAg) using a redox buffer.

In Rejection I, the examiner relies on Builder for disclosing the use of a redox buffer to "recover biologically active protein from cell culture." Answer, p. 4. The examiner argues that Builder discloses "adding 10mM GHS: 1mM GSSG to solubilize protein and incubating the mixture overnight at 37°C to permit the proper refolding into correct disulfide bond formation such as 10 mM GSH: 1mM GSSG, and incubating the protein and buffer at 37°C for 24 hours to permit proper refolding." Id., p. 5. According to the examiner, "[t]he purified protein exemplified by the method of Builder et al. has a much higher activity than unpurified protein." Id. The examiner acknowledges that Builder does not disclose purifying rHBsAg. To that end, the examiner relies on a publication by Valenzuela which is said to "establish that immunogenicity of HBsAg . . . strongly depends on the integrity and proper formation of disulfide bonds within the antigen." Id. The examiner points to pages 348-350 of Valenzuela for support.

It is well established that the examiner has the initial burden under § 103 to establish a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); In re Piasecki, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984). It is the examiner's responsibility to show that some objective teaching or suggestion in the applied prior art, or knowledge generally available [in the art] would have led one of ordinary skill in the art to combine the references to arrive at the claimed invention. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

Here, the examiner states that he is relying on the Valenzuela publication in Nature, vol. 280, pages 815-819 (1979)(hereinafter Valenzuela I). Answer, p. 4. The examiner's arguments, however, reference different page numbers; viz., pages 348-349. Going back over the prosecution, we find that this is not the only time that the examiner has made this argument. Attention is directed to the final office action, mailed November 5, 2003, and the non-final rejection mailed May 5, 2003, where the examiner references the same Nature publication [vol. 280] for the same reason. Given the aforementioned discrepancy in the page numbers, it does not appear that the examiner is relying on [or has ever relied upon] the publication listed on page 4 of the Answer.

In any event, turning to the Nature publication before us, we find that it is directed to the cloning of the HBV (hepatitis B virus) genome and the characterization of the surface antigen (HBsAg). That is, Valenzuela I discloses the nucleotide sequence of the HBsAg gene and the amino acid sequence deduced therefrom. With

respect to the disulfide bonds within the protein, we find that Valenzuela I discloses that the sequences flanking a hydrophobic region are rich in both proline and cysteine residues. Valenzuela I, p. 817, col. 1, lines 12-15. Valenzuela I suggests that "the abundant cysteine residues could make intra- and intermolecular linkages to form the surface coat of the virus." Id., lines 17-19. However, we find no teachings with respect to the expression of the HBsAg gene. Therefore, it reasonably follows that Valenzuela I does not describe the immunogenicity of the cloned HBsAg (rHBsAg) or the role of disulfide bonds with respect to the integrity of the antigen. Accordingly, since the examiner is clearly relying on a reference which is not before us, the rejection is summarily reversed.

Be that as it may, we neverthless searched the application file and found, of record,[1] another Nature publication by Valenzuela (Nature, vol. 298, pp. 347-350 (1982)(hereinafter Valenzuela II), which has the page numbers referred to in the examiner's rejection. Assuming, arguendo, that we were to consider this publication in the manner proposed by the examiner, we still could not affirm the rejection. Valenzuela II discloses the production of 22-nm surface antigen particles resulting from the expression of DNA encoding HBsAg in yeast. Valenzuela II further discloses that "[t]he predominant form of HBsAg produced by human cells is the so-called 22-nm particle. Its biophysical properties are well documented and its immunological potency

[1] See, "List of References cited by applicant and considered by the examiner," entered May 5, 2003.

exceeds that of the pure protein" [footnotes omitted]. Valenzuela II, p. 349, col. 1, first complete para. Valenzuela II still further discloses that the yeast-produced 22-nm HBsAg particles are "immunoreactive with anti-HBsAg antibodies" and that they "are similar to those made by human carrier patients or by a hepatoma cell line." Id., para bridging pp. 349-350. Valenzuela II concludes that "[t]he similarity in structure of the yeast particle to bona fide 22-nm particles and the high immunogenicity in animals emphasize the possible value of the HBsAg particle as a vaccine." Id., p. 350, col. 2, lines 3-5. Given this disclosure of the highly immunogenic nature of the yeast-produced rHBsAg particles and their possible use as a vaccine, we find no suggestion in Valenzuela II to modify the rHBsAg described therein in any manner. To the contrary, we find that the reference "teaches away" from any further modifications of rHBsAg.

We recognize that the examiner relied on Builder as the primary reference. However, we find that Builder is directed to the problems associated with expressing heterologous proteins in E. coli; viz., the recovery of heterologous proteins which are often "precipitated within the cell as 'refractile' bodies" in an inactive form. Builder, col. 1, lines 9-16. The appellants point out, and the examiner does not disagree, that the proteins in the refractile bodies disclosed by Builder are insoluble. See, e.g., the abstract; col. 2, lines 15-22; col. 12, lines 39-41. Builder further discloses that "drastic means is [sic, are] required to bring this protein into solution so that it can be used." Id., col. 2, lines 59-61. This is accomplished by using a strong denaturing solution which unfolds the protein and dissolves it into the [denaturing] solution. Id., col. 2, lines 61-62;

col. 7, lines 61-63; col. 9, lines 53-59 (Scheme 1); col. 12, lines 34-57. Since denatured proteins are not biologically active, Builder discloses, inter alia, a method of refolding the protein by incubating it in the presence of a redox buffer "at about 0° C to 37° C, depending on the protein, 4-24 hours, preferably overnight." Id., col. 16, lines 50-55; see also, col. 17, lines 43-50. We find no teaching or suggestion in Builder to use the methods described therein for treating soluble, biologically-active proteins. Thus, we do not find Builder would have suggested to one of ordinary skill in the art to incubate the soluble, biologically-active (immunogenic) HBsAg taught by Valenzuela II in the manner recited in the claims. Rather, on this record, the only suggestion we find to incubate soluble, sterile-filtered rHBsAg with a redox buffer at "about 34° C to about 38° C for about 40 to about 240 hours" is in the appellants' disclosure. Thus, we find that the examiner has engaged in impermissible hindsight to arrive at the conclusion that the claimed invention would have been obvious over Builder and Valenzuela I (or II). In re Fritch, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992); Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985); W.L. Gore & Assocs. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-313 (Fed. Cir. 1983) cert. denied 469 U.S. 851 (1984)("To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher").

Rejections I and II are based on the premise that the subject matter of claim 8-16 would have been obvious to one of ordinary skill in the art in view of the combined teachings of Building and Valenzuela. Since we find that the references fail to render said claims obvious, it follows that these rejections cannot be affirmed.

In view of the foregoing, the decision of the examiner is reversed.

REVERSED

Joan Ellis
Administrative Patent Judge)
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Toni R. Scheiner) BOARD OF PATENT
Administrative Patent Judge)
) APPEALS AND
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Eric Grimes) INTERFERENCES
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